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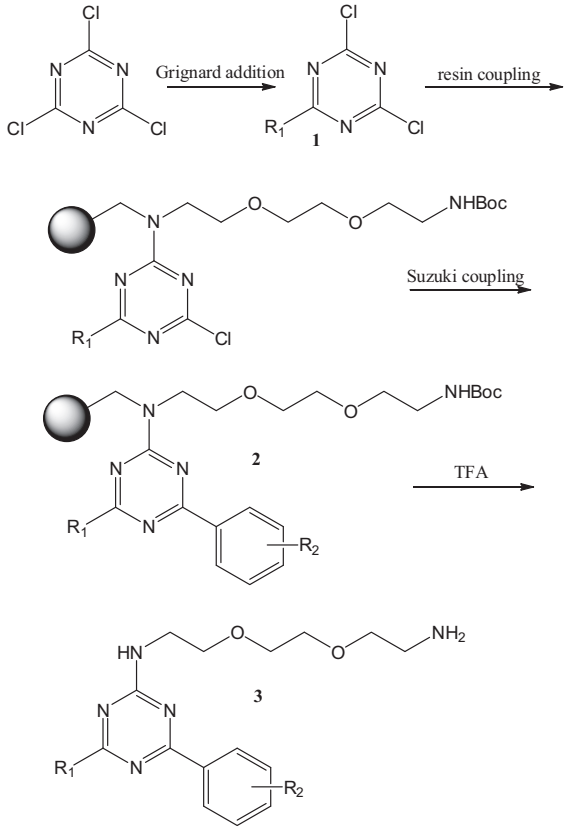
1. Current literature highlights

1.1. Combinatorial synthesis of 4,6-diaryl and 4-aryl, 6-alkyl-1,3,5-triazines and their application to biofuel production

Substituted 1,3,5-triazines can be readily synthesised by the reaction of amines, alcohols or thiols with cyanuric chloride, to insert groups via a carbon-heteroatom bond. Reactions of the triazine scaffold forming carbon–carbon bonds have been much less well explored. Given the frequency of aryl–aryl motifs in drug molecules, and their categorisation as privileged structures, it is surprising that there have been very few examples of diaryl or aryl, alkyl substituted triazines. The introduction of carbon substituents via either Grignard reagents or Suzuki couplings has been recently reported, and this methodology has now been extended to the preparation of a triazine library with potential utility for improving biofuel generation.[1]

Lipids are ubiquitous in living organisms, and their synthesis in microorganisms and plants offers the potential for sustainable fuel sources. In order to improve yields, genetic approaches have been investigated, and small molecules have been investigated that modify lipid accumulation. A focus of this study was *Yarrowia lipolytica*, a yeast that is recognised for its versatile lipid biosynthetic pathways. A library of substituted triazines was synthesised and screened for the ability of the product compounds to regulate biolipid production.

A library of compounds was generated in a two-step process through a solution-phase Grignard addition followed by a solid-phase Suzuki coupling. Cyanuric chloride was derivitised by 12 different Grignard reagents to introduce both aryl and alkyl groups onto the 6-position to give product **1**. These products were loaded onto an amine-derivatised PAL-polystyrene resin and reacted with 10 different boronic acids under Suzuki coupling conditions. The products **2** were cleaved from resin by treatment with TFA to give the final library components **3** in around 90% purity without any purification step.



Each compound was then tested for its ability to promote lipid accumulation in *Y. lipolytica*, analysing the lipid content by staining the cells with a lipid sensing dye. Only one compound (**4**) in the library of 120 compounds was found to produce a significant

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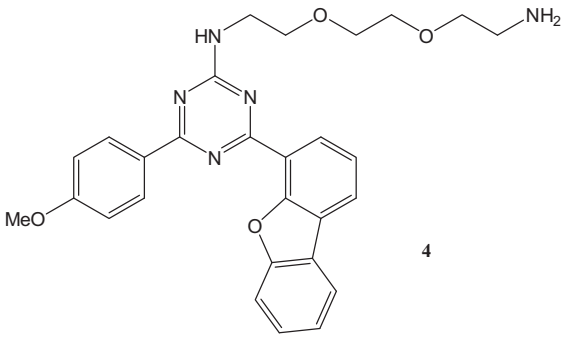
increase in lipids. It was subsequently determined by the synthesis of close analogues that the ethyleneglycol chain was not a major contributor to the effect on lipid accumulation.



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It was demonstrated that cells treated with the active compounds produce more triglyceride than DMSO-treated control cells. None of the compounds showed any significant toxicity or were responsible for cell growth inhibition. The mechanism by which the lipid accumulation was stimulated in *Y. lipolytica* is currently being investigated.

2. A summary of the papers in this month's issue

2.1. Polymer supported synthesis

An efficient method for the synthesis of *N*,*N*′-di(Boc)-protected guanidines containing piperazine and homopiperazine scaffolds has been developed. The approach proceeded via deprotonation of the acidic N-carbamate hydrogen of the guanidine on a soluble polymer support, followed by alkylation using various alkyl halides under multi-step microwave irradiation.[2]

2.2. Solution-phase synthesis

No papers this month.

2.3. Scaffolds and synthons for combinatorial libraries

No papers this month.

2.4. Solid-phase supported reagents

A simple, efficient one-step route to polystyrene-supported trialkylphosphine ligands has been reported. These polymer-supported alkyl phosphine ligands have proven to be highly active for Suzuki–Miyaura reactions and in alkoxycarbonylation reactions. The palladium loaded polymer-supported catalysts can be recycled several times with only minimal loss of catalyst activity.[3]

An efficient and highly selective synthesis of functionalised 1,2-benzimidazoles has been developed under solvent-free conditions at ambient temperature using ferric sulphate soaked with silica [iron(III)sulphate–silica]. Recycling of the solid supported reagent for up to six runs was investigated with appreciable yield and selectivity of the product.[4]

The Swern oxidation of various benzylic and allylic alcohols, primary alcohols, and secondary alcohols with two ion-supported methyl sulphoxides and oxalyl chloride has given the corresponding aldehydes and ketones, respectively, in good yields and with high purity. Similarly, the Corey–Kim oxidation of various benzylic and allylic alcohols, primary alcohols, and secondary alcohols with two ion-supported methyl sulphides and *N*-chlorosuccinimide has given the same oxidation products. Neither reaction produced any unpleasant odour, and in the Swern oxidation, ion-supported methyl sulphides were recovered in high yields and could be re-oxidised to produce ion-supported methyl sulphoxides for reuse.[5]

2.5. Novel resins, linkers and techniques

Combinatorial library design has been dramatically changed by the introduction of multi-objective optimisation, which can consider many objectives simultaneously, such as synthesis cost and drug-likeness. A recent publication describes Combinatorial Chemistry Laboratory (CCLab) – software for library design based on a multi-objective genetic algorithm. The program was applied to a real case of designing an histone deacetylase (HDAC) inhibitor library. Sixteen compounds in the library were synthesised, and the enzymatic assays proved that CCLab could enhance the hit rates of the designed library.[6]

Dramatically improved total syntheses of two highly selective V600EBRAF inhibitors, PLX4720 and PLX4032, using microwave-assisted organic synthesis (MAOS) have been reported. Compared with previously reported approaches, the novel MAOS method significantly reduces overall reaction time without compromising yield. In addition to providing a gram-scale route to these compounds for preclinical oncology research, this approach could accelerate the synthesis of azaindoles in high-throughput, library-based formats.[7]

2.6. Library applications

A small library of 3,5-disubstituted-1,2,4-oxadiazole containing combretastatin A-4 (CA-4) analogues has been designed and synthesised, with the objective of increasing the efficacy of CA-4 as an anti-tubulin and antimitotic agent. These compounds were synthesised via a coupling reaction between an amidoxime and a carboxylic acid, and using this protocol, a small library of 10 compounds were prepared in moderate to good yields. A detailed biological study is currently ongoing to evaluate the activity of these compounds.[8]

A recent paper has demonstrated that reverse transcriptase can be inhibited by molecules (e.g. intercalators) that target the key RNA/DNA duplex substrate. The lead intercalators can be modified to increase inhibition efficacy by the strategy of multiple simultaneous intercalation, by linking two intercalators with a variable linker. A library of 45 ethidium bis-intercalators in which the distance between intercalators is systematically varied has been prepared, and members of the dimer library have improved telomerase and reverse transcriptase inhibition, relative to the monomeric leads.[9]

Using a compound library screening approach, a novel series of disubstituted benzamide compounds with significant activity against malaria strains 3D7 and K1 has been discovered. These compounds represent a new antimalarial molecular scaffold, which demonstrated EC_{50} values of 60 and 430 nM against strains 3D7 and K1 respectively.[10]

A library of 1,3-disubstituted 2-propanols has been synthesised and evaluated as low molecular weight probes for β-secretase inhibition. Screening a library of 121 1,3-disubstituted 2-propanol derivatives, resulted in the identification of a few compounds inhibiting the enzyme at low micromolar concentrations. The initial hits were optimised to yield a potent BACE-1 inhibitor exhibiting an IC_{50} constant in the nanomolar range. These small molecular inhibitors possessed a high selectivity over cathepsin D and desirable physicochemical properties beneficial to cross the blood–brain barrier.[11]

Optimisation of the MLSCN/MLPCN probe ML077 (neuronal-specific potassium-chloride cotransporter 2 (KCC2) IC_{50} = 537 nM)

has proven to be challenging as the results revealed a steep SAR. However, a multi-dimensional iterative parallel synthesis approach proved more productive. Specifically, the discovery and SAR of an improved novel antagonist (VU0463271) of the KCC2 has been reported. This compound has an IC_{50} of 61 nM and >100-fold selectivity versus the closely related Na-K-2Cl co-transporter 1 (NKCC1) and no activity in a larger panel of GPCRs, ion channels and transporters.[12]

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